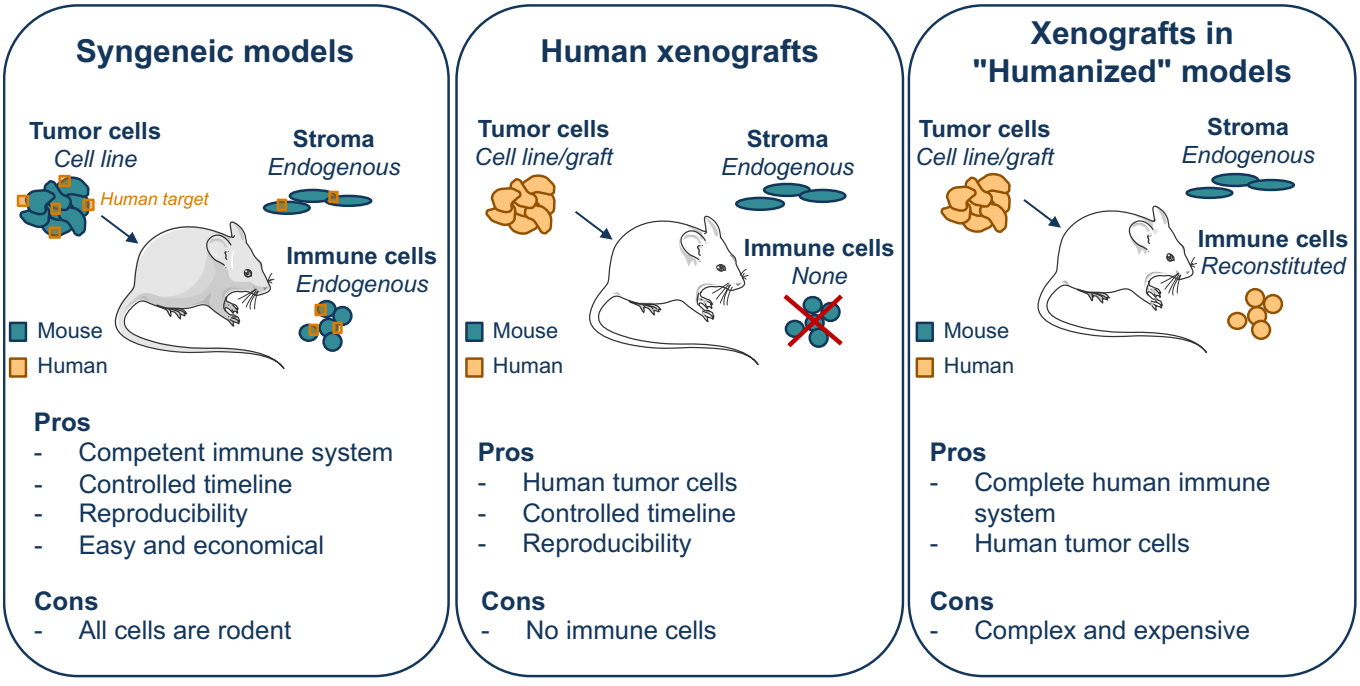
Tumor grafts in preclinical research: Models, models, overall, who's the fittest of them all?

Commentary by Amélie Rezza, PhD, & Alessia Armezzani, PhD 31/08/2021

As in all experimental research areas, drug development in oncology largely relies on preclinical models, particularly rodent models such as the mouse and rat. The most common experimental rodent models in oncology feature transplantable tumors in which a recipient animal is injected with tumor cells.[1] There is a variety of transplantable tumor models available today, depending on the type of recipient used (immunocompetent or immunocompromised) and the type of tumor cells implanted (tumor cell lines or tumors from patients).

In syngeneic models (left panel), mouse or rat tumor cell lines are implanted in an immunocompetent recipient of the same genetic background, representing a type of allograft. In this specific tumor model system, all cells—tumor, immune and stromal (representing the tumor microenvironment)—are from the same rodent species. It allows one to tightly control experimental timelines as it is very reproducible and it is cost effective. With the development of efficient gene editing tools, it is now possible to optimize further syngeneic models through genetic humanization of a specific target of interest. In that case, injected tumor cells and/or the recipient's cells, express a human version of the gene of interest, although in a rodent system.



Immunodeficient rodents strains have also been developed and are now commonly used as xenograft recipients (central panel). As they have an impaired immune system, human cells can be implanted to form tumors, allowing the study of human tumor markers and physiology. Here, again, stromal cells are rodent. Although very useful for mechanism-of-action studies, these models present a major drawback for some applications: they have an impaired immune system.

To increase translatability and work in a model with human immune cells, immunocompromised recipients can be reconstituted with a human immune system (right panel). Human tumor cells can then be implanted in these reconstituted recipients, where only stromal cells remain rodent. These models have a high translatability, as most cells in the tumor are of human origin, but they are still a little challenging to work with, and rather expensive.

All these models have pros and cons, and they present varying levels of physiological relevance, complexity, and thus cost. Interestingly, different models are actually useful for different applications.

In immunotherapy, where targeted cells are immune cells, the recipients must present an immune system. This is one of the reasons why syngeneic models are largely used in immuno-oncology. Genetically humanized models, carrying a human version of a target, can be used as recipient in an optimized syngeneic system. For example, genetically humanized rodents can provide a reliable recipient model to study the efficacy and toxicity of bispecific antibodies.[2,3] These genetically humanized recipients can even be injected with a "humanized" syngeneic cell line to provide a model with both immune and tumor human targets. Alternatively, human tumor xenografts in reconstituted mice with a human immune system also represent a versatile model to perform efficacy and toxicity studies of immunotherapeutics.[4,5]

For other anti-tumor treatments, where the immune system is not the primary target, cell line-derived xenografts (immunocompromised mice implanted with human cell lines), and patient-derived xenografts (immunocompromised mice implanted tumor cells from patients) are particularly interesting. Indeed, immune cells are not required for mechanism of action and preliminary efficacy studies of this kind of therapeutics. Interestingly, immunocompromised rats are also available and can represent a preferable model for certain research areas or applications.

In addition to efficacy and toxicity studies, drug development also includes pharmacokinetics (PK) and pharmacodynamics (PD) studies. Recently, an immunocompromised model of PK/PD was developed for testing albumin-based therapeutics: HSA/hFcRn/Rag1-KO.[6] This model allows for the development of tumors in humanized HSA/hFcRn mice, thus permitting one to perform PK/PD studies of anti-tumor HSA-based compounds.

Overall, the entire drug development pipeline in oncology is strongly affected by the availability of reliable preclinical animal models. Numerous tumor-graft models are available and used today. Indeed, depending on the application, a "simple" syngeneic model might be the optimal system, whereas for others, a reconstituted xenograft model would be necessary. Lastly, although a vast diversity of animal models is already available for oncology research, new models are constantly being generated to improve relevance and, hopefully, translatability to patients.

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